

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



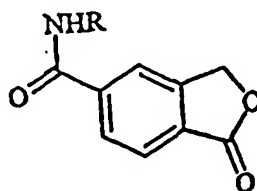
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 307/87	A1	(11) International Publication Number: WO 00/39112 (43) International Publication Date: 6 July 2000 (06.07.00)
<p>(21) International Application Number: PCT/DK99/00728</p> <p>(22) International Filing Date: 22 December 1999 (22.12.99)</p> <p>(30) Priority Data: PA 1998 01718 23 December 1998 (23.12.98) DK</p> <p>(71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby Copenhagen (DK).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). DAHLBERG NIELSEN, Poul [DK/DK]; Prejlerupvej 26, DK-4560 Vig (DK).</p> <p>(74) Common Representative: H. LUNDBECK A/S; Petersen, John, Heidahl, Ottiliavej 9, DK-2500 Valby Copenhagen (DK).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KO, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: METHOD FOR THE PREPARATION OF 5-CYANOPHTHALIDE

(57) Abstract

A method for the preparation of 5-cyanophthalide in which 5-carboxyphthalide is converted to the corresponding amide of Formula (IV) in which R is hydrogen or C<sub>1-6</sub> alkyl, which is then reacted with a dehydrating agent thereby obtaining 5-cyanophthalide. The conversion of 5-carboxyphthalide to the corresponding amide of Formula (IV) may be carried out via the corresponding C<sub>1-6</sub> alkyl or phenyl ester or the acid chloride, which is converted to the amide of Formula (IV) by amidation with ammonia or a C<sub>1-6</sub> alkylamine. By the process 5-Cyanophthalide, an important intermediate used in the preparation of the antidepressant drug citalopram, is prepared in high yields by a convenient, cost effective procedure.



(IV)

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

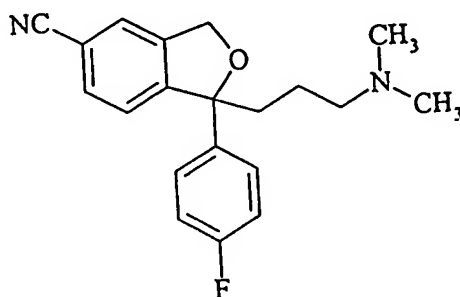
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	R	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

# METHOD FOR THE PREPARATION OF 5-CYANOPHTHALIDE

The present invention relates to a novel process for the preparation of 5-cyanophthalide which is an intermediate used in the manufacture of the well known antidepressant drug  
5 citalopram,  
isobenzofurancarbonitrile.

## Background of the Invention.

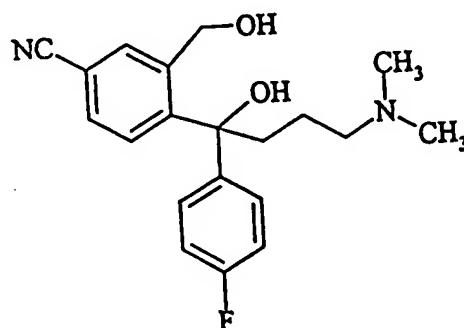
10 Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

15 It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 1982, 6, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, 1987, 75, 478-486.

20 Citalopram is prepared by the process described in US Patent No 4,650,884, according to which 5-cyanophthalide is subjected to two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively, and the resulting compound of the formula



Formula II

25

is subjected to a ring closure reaction by dehydration with strong sulfuric acid.

Enantiomers of citalopram may be prepared by the method described in US Patent No. 4,943,590, i.e. by separating the enantiomers of the intermediate of Formula II and performing enantioselective ring closure in order to obtain the desired enantiomer.

- 5 Thus, 5-cyanophthalide is an important intermediate for the manufacture of citalopram and it is important to produce this material in an adequate quality, by a convenient process and in a cost-effective way.

- 10 A method for the preparation of 5-cyanophthalide has previously been described in Bull. Soc. Sci. Bretagne, 26, 1951, 35 and in Levy and Stephen, J. Chem. Soc., 1931, 867. By this method, 5-aminophthalide is converted to the corresponding 5-cyanophthalide by diazotation followed by reaction with CuCN. 5-Aminophthalide was obtained from 4-aminophthalimide by a two step reduction procedure.

- 15 Synthesis of certain alkyl- and phenylnitriles from acid chlorides is described in Tetrahedron Letters, 1982, 23, 14, 1505 - 1508, and in Tetrahedron, 1998, 54, 9281.

Though a number of other methods failed, it has been found that 5-cyanophthalide may be prepared in high yields by a convenient, cost-effective procedure from 5-carboxyphthalide.

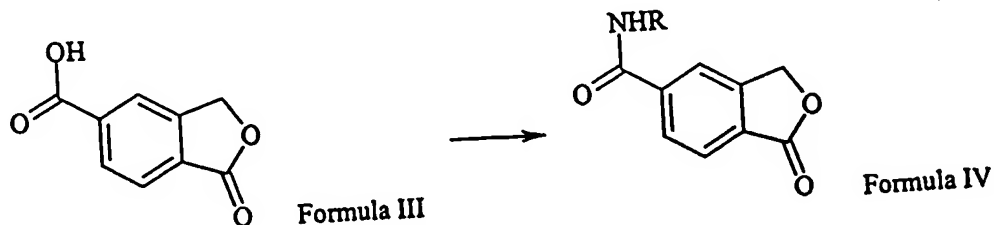
20

### Description of the invention

Accordingly, the present invention provides a novel method for the preparation of 5-cyanophthalide from 5-carboxyphthalide comprising

25

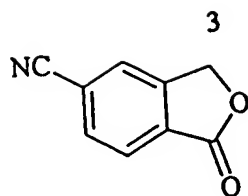
- a) converting 5-carboxyphthalide to an amide of Formula IV



in which R is hydrogen or C<sub>1-6</sub> alkyl, and

30

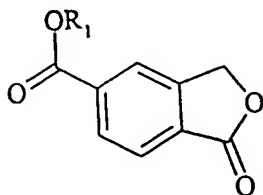
- b) then reacting the amide of Formula IV with a dehydrating agent thereby obtaining 5-cyanophthalide



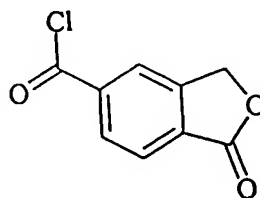
Formula V

The conversion of 5-carboxyphthalide to the amide of Formula IV may be carried out via an ester of Formula VI or an acid chloride of Formula VII or via the ester and the acid chloride:

5



Formula VI



Formula VII

wherein  $R_1$  is  $C_{1-6}$  alkyl or phenyl. The acid chloride is conveniently obtained by treatment of 5-carboxyphthalide with  $POCl_3$ ,  $PCl_5$  or  $SOCl_2$  neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of  $N,N$ -dimethylformamide. The ester is obtained by treatment of 5-carboxyphthalide with an alcohol  $R_1OH$ , wherein  $R_1$  is as defined above, in the presence of an acid, preferably a mineral acid or a Lewis acid, such as  $HCl$ ,  $H_2SO_4$ ,  $POCl_3$ ,  $PCl_5$  or  $SOCl_2$ . Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol. The ester of Formula VI or the acid chloride of Formula VII is then converted to the amide of Formula IV by amidation with ammonia or an  $C_{1-6}$  alkylamine, preferably  $t$ -butyl amine.

Throughout the specification and Claims,  $C_{1-6}$  alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

The dehydrating agent used in step b) may be any suitable dehydrating agent, and the optimal agent may easily be determined by a person skilled in the art. Examples of suitable dehydrating agents are  $SOCl_2$ ,  $POCl_3$  and  $PCl_5$ , preferably  $SOCl_2$ .

25

The reaction in step b) is carried out neat or in a suitable solvent, such as toluene, sulfolan or conveniently acetonitrile. When the reaction is carried out in a solvent, 1.0 - 1.5, preferably 1.0 - 1.2 equivalents of dehydrating agent is used per equivalent of the amide of Formula V. Furthermore, when a solvent is used, a catalytic amount of  $N,N$ -dimethylformamide may be needed, in particular when the dehydrating agent is  $SOCl_2$ . Preferably, toluene is used as the solvent, if necessary in the presence of a catalytic amount of  $N,N$ -dimethylformamide.

30

WO 00/39112

4

The reaction in step b) is carried out at elevated temperature, preferably at the reflux temperature of the solvent.

The reaction time is not important and may easily be determined by a person skilled in the art.

5 5-Cyanophthalide may be isolated in a conventional way, e.g. by addition of water, filtration and subsequent washing of the crystals. Further purification may, if desired, be performed by recrystallisation.

10 In a preferred embodiment of the process of the invention, R in Formula IV is H or t-butyl. When the reaction in step a) is carried out via an ester, R<sub>1</sub> is preferably methyl or ethyl.

15 In a particularly preferred embodiment of the invention 5-carboxyphthalide of Formula III is reacted with an alcohol, R<sub>1</sub>OH, preferably ethanol, in the presence of POCl<sub>3</sub>, in order to obtain the corresponding ester of Formula VI, which is then reacted with ammonia thereby giving 5-carbamoylphthalide, which in turn is reacted with SOCl<sub>2</sub> in toluene comprising a catalytic amount of N,N-dimethylformamide.

20 Surprisingly, substantially no reaction takes place at the lactone ring. Accordingly, by the process of the invention, 5-cyanophthalide is obtained in high yields and the process is much more convenient than the known process and uses more convenient and cheaper reactants and conditions.

25 The 5-carboxyphthalide used as a starting material may be obtained by the methods described in US patent No. 3,607,884 or German patent No. 2630927, i.e. by reacting a concentrated solution of terephthalic acid with formaldehyde in liquid SO<sub>3</sub> or by electrochemical hydrogenation of trimellithic acid.

### Examples

30 The invention is further illustrated by the following examples.

#### Example 1

##### Preparation of 5-Cyanophthalid

##### 35 5-Chlorocarbonylphthalid

5-Carboxyphthalid (53 g, 0.3 mole) was suspended in toluene (200 mL) and thionylchloride (44 g, 0.6 mole). N,N-dimethylformamide (DMF) (1 mL) was added and the mixture was heated at reflux temperature for 3 hours. The mixture was cooled to room temperature and n-heptane was added (200 mL). The crystals formed were collected and washed with

heptane (100 mL). Yield 52 g, 88%. DSC onset: 131 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): 5.47 (2H, s), 8.06 (1H, d, J = 7.5 Hz), 8.28 (1H, d, J = 7.5 Hz), 8.3 (1H, s). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): 69.4, 125.1, 126.1, 131.1, 131.6, 137.8, 146.6, 167.4, 169.0.

5 **5-tert-Butylcarbamyphthalid**

Method A):

5-Carboxyphthalid (36 g, 0.2 mole) was suspended in thionylchloride (100 mL). DMF (1.5 mL) was added and the mixture was refluxed for 1 hour. Toluene (200 mL) was added and the solvents were evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (THF) (200 mL) and added to a solution of tert-butylamine (31 g, 0.42 mole) in THF (200 mL) at 5 °C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was then poured into ice water (400 mL) and the precipitated crystals were filtered off. The crystals were washed with water (100 mL). Yield: 41 g, 87%. DSC onset: 189.5 °C.

15 Method B):

A solution of 5-chlorocarbonylphthalid (39 g, 0.2 mole) in THF (200 mL) was added to a solution of tert-butylamine (19 g, 0.25 mole) and triethylamine (26 g, 0.25 mole) in THF (200 mL) at room temperature. The mixture was stirred for 1 hour. The reaction mixture was then poured into ice water (500 mL). The crystalline material formed was collected and washed with water (100 mL).

20 Yield 42.5 g, 91%. DSC onset: 192 °C. Purity: 99.5% (hplc, peak area). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): 1.4 (9H, s), 5.46 (2H, s), 7.88 (1H, d, J = 7.5 Hz), 7.95 (1H, d, J = 7.5 Hz), 8.04 (1H, s). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 125 MHz): 28.5, 51.2, 70.0, 122.0, 124.6, 126.6, 128.2, 141.3, 147.2, 165.5, 170.1.

25

**5-Ethoxycarbonylphthalid**

Method A):

5-Carboxyphthalid (37 g, 0.2 mole) was suspended in ethanol (400 mL). POCl<sub>3</sub> (10 g, 0.07 mole) was added drop-wise and the reaction mixture was heated to reflux temperature for 5 hours. Upon cooling to room temperature, the title compound crystallised. The crystals were filtered off and washed with ethanol (50 ml). Yield: 35 g, 87%. DSC onset: 151 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 250 MHz): 1.36 (3H, t, J = 7 Hz), 4.38 (2H, q, J = 7 Hz), 5.48 (2H, s), 7.95 (1H, d, J = 7.5 Hz), 8.12 (1H, d, J = 7.5 Hz). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 62.5 MHz): 14.5, 61.5, 70.1, 124.0, 125.2, 128.8, 129.6, 134.8, 147.6, 164.9, 169.8.

35

Method B):

5-Chlorocarbonylphthalid (39 g, 0.2 mole) was suspended in ethanol (200 mL). The



mixture was heated to reflux for 15 minutes. After cooling, the crystalline material formed was filtered off and washed with ethanol (50 ml). Yield: 36 g, 88%. DSC onset: 151 °C.

### 5-Carbamylphthalid.

#### 5 Method A):

5-Ethoxycarbonylphthalid (41 g, 0.2 mole) was suspended in ammonia (10M solution in methanol, 200 mL) in a pressure reactor. The reaction temperature was held at 80 °C for 20 hours. After cooling, the reaction mixture was poured onto ice (250 g) and pH was adjusted to pH=1 using concentrated hydrochloric acid. The mixture was stirred for 2 hours. The crystals formed were filtered off and washed with water (4x100 mL) and dried *in vacuo*. Yield: 33 g, 93%. DSC onset: 237 °C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 250 MHz): 5.47 (2H, s), 7.65 (1H, s (NH)), 7.92 (1H, d, J=7.5 Hz), 8.06 (1H, d, J=7.5 Hz), 8.14 (1H, s), 8.22 (1H, s (NH)). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 62.5 MHz): 70.0, 122.2, 124.9, 127.2, 128.2, 139.7, 147.4, 167.1, 170.1.

#### 15 Method B):

5-Chlorocarbonylphthalid (20 g, 0.1 mole) was dissolved in THF (100 mL) and added to ammonium hydroxide (50 mL) in ice water (300 mL). The mixture was stirred for 30 minutes and the precipitated crystals were filtered off. The crystals were washed with water (100 mL) and dried *in vacuo*. Yield: 17.1 g, 97%. DSC onset: 237 °C.

### 5-Cyanophthalid.

#### Method A):

Dry 5-carbamylphthalid (36 g, 0.2 mole) was suspended in toluene (600 mL) and thionylchloride (36 g, 0.3 mole) was added. DMF (2 mL) was added. The reaction mixture was heated at 75 °C for 6 hours. Toluene (100 mL) was removed by distillation and the remaining solution was cooled to room temperature. The crystals formed were filtered off and washed with toluene (150 mL) and water (100 mL). The product was recrystallised from toluene. Yield: 22 g, 80%. DSC onset: 203 °C.

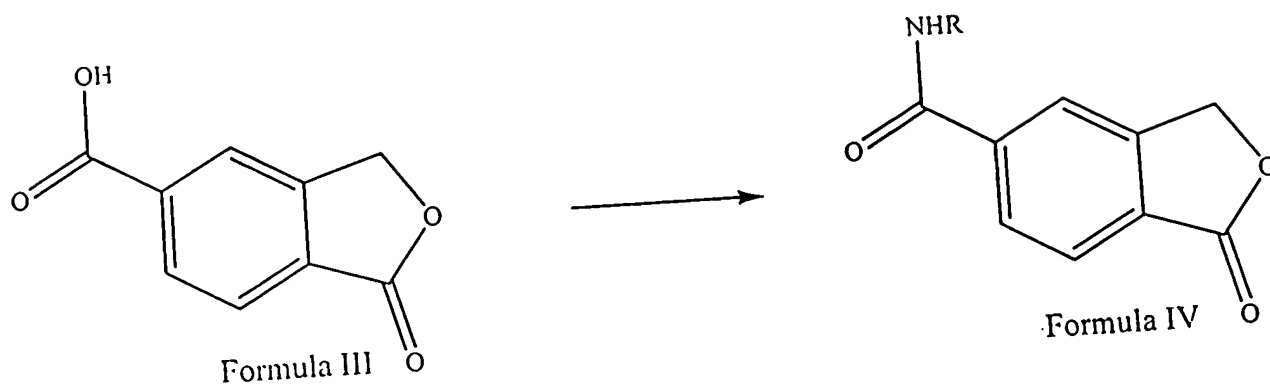
#### 30 Method B):

Tert.-Butylcabamylphthalid (23.3 g, 0.1 mole) was suspended in thionylchloride (100 mL). The mixture was heated to reflux for 30 min. Toluene (100 mL) was added and the solvents were removed *in vacuo*. The title product was crystallised from acetic acid or toluene.

Yield 15.5 g, 93% from toluene. DSC onset: 203 °C. Purity: 98% (hplc, peak area).

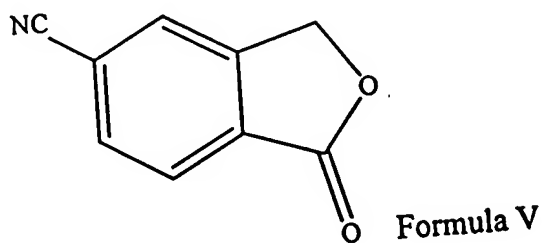
## CLAIMS

1. A method for the preparation of 5-cyanophthalide comprising
  - a) conversion of a 5-carboxyphthalide to an amide of Formula IV

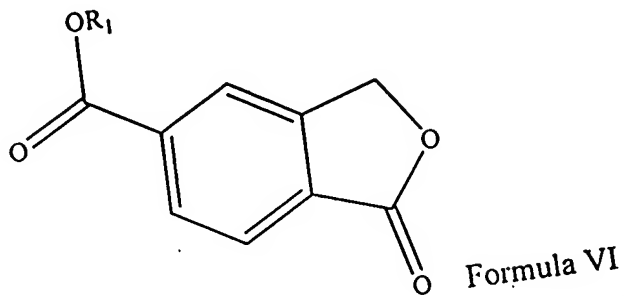


in which R is hydrogen or C<sub>1-6</sub> alkyl, and

- b) then reacting the amide of Formula IV with a dehydrating agent thereby obtaining 5-cyanophthalide

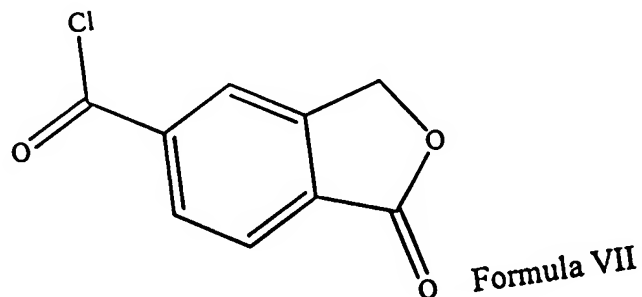


2. The method of claim 1, wherein the conversion of 5-carboxyphthalide to the amide of Formula IV is carried out via an ester of Formula VI:



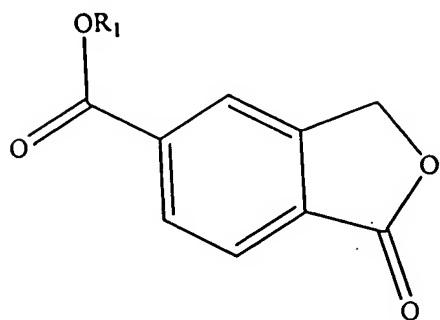
wherein  $R_1$  is  $C_{1-6}$  alkyl or phenyl, by treatment of 5-carboxyphthalide with an alcohol  $R_1OH$  in the presence of an acid and subsequent amidation of the ester of formula VI with ammonia or a  $C_{1-6}$  alkylamine.

3. The method of claim 1, wherein the conversion of 5-carboxyphthalide to the amide of Formula IV is carried out via an acid chloride of Formula VII:

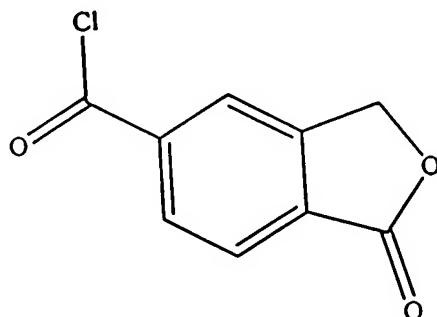


by treatment of 5-carboxyphthalide with  $POCl_3$ ,  $PCl_5$ , or  $SOCl_2$  and subsequent amidation of the acid chloride of Formula VII with ammonia or a  $C_{1-6}$  alkylamine.

4. The method of claim 1, wherein the conversion of 5-carboxyphthalide to the amide of Formula IV is carried out via an acid chloride of Formula VII and an ester of Formula VI:



Formula VI



Formula VII

wherein  $R_1$  is  $C_{1-6}$  alkyl or phenyl, by treatment of 5-carboxyphthalide with  $POCl_3$ ,  $PCl_5$ , or  $SOCl_2$ , reacting the acid chloride of Formula VII thus formed with an alcohol  $R_1OH$  and performing amidation of the ester of Formula VI with ammonia or a  $C_{1-6}$  alkylamine.

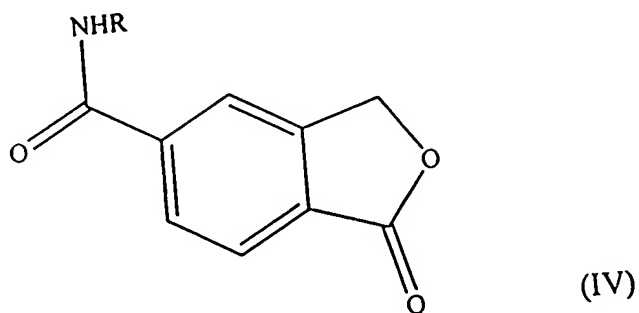
5. The method of claim 2, wherein the acid used is a mineral acid or Lewis acid.
6. The method of claim 5, wherein the mineral acid or Lewis acid is selected from the group consisting of  $HCl$ ,  $H_2SO_4$ ,  $POCl_3$ ,  $PCl_5$ , and  $SOCl_2$ .
7. The method of claim 2, 4 or 5, wherein  $R_1$  is methyl or ethyl.
8. The method of claim 1, in which the dehydrating agent used in step b) is  $SOCl_2$ ,  $POCl_3$ , or  $PCl_5$ .

9. The method of claim 8, in which the dehydrating agent is  $\text{SOCl}_2$ .
10. The method of claim 1, wherein the reaction in step b) is carried out neat or in a suitable solvent.
11. The method of claim 10, wherein the reaction is carried out in a solvent selected from the group consisting of toluene, sulfolan or acetonitrile.
12. The method of claim 11, wherein the solvent is toluene.
13. The method of claim 10, wherein the dehydrating agent used in step b) is  $\text{SOCl}_2$  and the reaction is carried out in toluene comprising a catalytic amount of N,N-dimethylformamide.
14. The method of claim 1, wherein R is H or tert-butyl.
15. The method of claim 2, wherein the 5-carboxyphthalide of Formula III is reacted with an alcohol  $\text{R}_1\text{OH}$ , in the presence of  $\text{POCl}_3$ , in order to obtain an ester of Formula VI, which is then reacted with ammonia, thereby giving 5-carbamoyl-phthalide, which in turn is reacted with  $\text{SOCl}_2$  to 5-cyanophthalide.
16. The method of claim 15, wherein the alcohol  $\text{R}_1\text{OH}$  is ethanol or methanol.

17. The method of claim 15, wherein the 5-carboxyphthalide of Formula III is reacted with ethanol in the presence of  $\text{POCl}_3$ , in order to obtain the ethyl ester of Formula VI, which is then reacted with ammonia in methanol, thereby giving 5-carbamoylphthalide, which in turn is reacted with  $\text{SOCl}_2$  to 5-cyanophthalide.

**ABSTRACT**

A method for the preparation of 5-cyanophthalide in which 5-carboxyphthalide is converted to the corresponding amide of Formula (IV)



in which R is hydrogen or  $C_{1-6}$  alkyl, which is then reacted with a dehydrating agent thereby obtaining 5-cyanophthalide. The conversion of 5-carboxyphthalide to the corresponding amide of Formula (IV) may be carried out via the corresponding  $C_{1-6}$  alkyl or phenyl ester or the acid chloride, which is converted to the amide of Formula (IV) by amidation with ammonia or a  $C_{1-6}$  alkylamine. By the process 5-cyanophthalide, an important intermediate used in the preparation of the antidepressant citalopram, is prepared in high yields by a convenient, cost effective procedure.